Journal of Clinical Lipidology (2015) 9, 400–405

Journal of Clinical Lipidology

The Janus-faced manifestations of homozygous familial hypobetalipoproteinemia due to apolipoprotein B truncations

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KEYWORDS:
Apolipoprotein B;
Hypocholesterolemia;
Familial hypobetalipoproteinemia;
Liver steatosis;
Truncated apoB

Abstract: Familial hypobetalipoproteinemia is a codominant disorder characterized by low plasma levels of low-density lipoprotein cholesterol and apolipoprotein B (apoB), which in ~50% of the cases is due to mutations in *APOB* gene. In most cases, these mutations cause the formation of truncated apoBs of various sizes, which have a reduced capacity to bind lipids and form lipoprotein particles. Here, we describe 2 children with severe hypobetalipoproteinemia found to be homozygous for novel *APOB* gene mutations. The first case (HBL-201) was an asymptomatic 13-year-old boy incidentally found to have slightly elevated serum transaminases associated with hepatic steatosis. He was homozygous for a truncated apoB (2211 amino acids, apoB-48.74) whose size is similar to that of wild-type apoB-48 (2152 amino acids) produced by the intestine. ApoB-48.74 is expected to be incorporated into chylomicrons in the intestine but might have a reduced capacity to form secretion-competent very low–density lipoprotein in the liver. The second patient (HBL-96) was a 6-month-old girl suspected to have abetalipoproteinemia, for the presence of chronic diarrhea, failure to thrive, extremely severe hypobetalipoproteinemia, and low plasma levels of vitamin E and vitamin A. She was homozygous for a nonsense mutation (Gln513*) resulting in a short truncated apoB (apoB-11.30), which is not secreted into the plasma. In this patient, the impaired chylomicron formation is responsible for the severe clinical manifestations and growth retardation. In homozygous familial hypobetalipoproteinemia, the capacity of truncated apoBs to form chylomicrons is the major factor, which affects the severity of the clinical manifestations.

Introduction

Familial hypobetalipoproteinemia (FHBL, OMIM 615558) is a codominant disorder characterized by plasma levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apoB) below the fifth percentile of the

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Submitted September 28, 2014. Accepted for publication January 18, 2015.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2015.01.005

general population.[1] FHBL is genetically heterogeneous; it may be due to mutations in *APOB* gene (*APOB*-linked FHBL) or, less frequently, to loss of function mutations in *PCSK9* gene (*PCSK9*-linked FHBL). However, in many subjects the genetic basis of FHBL remains unexplained (orphan FHBL).[2] Most *APOB* gene mutations lead to the formation of C-terminally truncated forms of apoB of various sizes.[1–3] These truncated apoBs are designated according to a centile nomenclature with respect to apoB-100, the normal protein of 4536 amino acids, corresponding to the full-length translation product of apoB messenger RNA (mRNA), which is synthesized by the liver as constituent of very low–density lipoprotein (VLDL). Truncated apoBs lose, to a variable extent, the capacity to form plasma lipoproteins in liver and/or intestine and to export lipids from these organs.[1,2] Few nonconservative amino acid substitutions located in the NH_2-terminal end of apoB have been reported to be the cause of FHBL.[4–6] These missense mutations are associated with a decreased assembly and/or secretion of apoB-containing lipoproteins. Subjects with FHBL attributable to either truncating or missense mutations of apoB are prone to develop liver steatosis (non-alcoholic fatty liver disease [NAFLD]) due to the impaired secretion of VLDL by the liver.[1–3,7,8] FHBL heterozygotes may be asymptomatic or have NAFLD as the main clinical manifestation.[1–3,7–9] Mild intestinal lipid malabsorption and chronic diarrhea, exacerbated by fat-rich meals, have been reported in some FHBL heterozygotes carrying truncated apoBs shorter than apoB-48[3,9] because of a reduced postprandial production of triglyceride-rich lipoproteins by the intestine.[10]

Homozygous FHBL (Ho-FHBL), due to homozygosity and/or compound heterozygosity for *APOB* mutations, is a rare disorder characterized by plasma LDL-C and apoB levels either undetectable or ranging from 10% to 20% of the control values.[2]

The clinical phenotype of patients with Ho-FHBL due to *APOB* gene mutations shows a great variability. Some patients are asymptomatic or have mild NAFLD, whereas others have severe NAFLD, intestinal fat malabsorption, failure to thrive, and neurologic and ocular dysfunctions[2] as observed in patients with abetalipoproteinemia (ABL, OMIM 200100; a recessive disorder due to mutations in *MTTP* gene).[11]

Herein, we describe 2 Turkish children with severe hypobetalipoproteinemia who were found to be homozygous for 2 novel mutations in *APOB* gene resulting in truncated apoBs but showing a strikingly different clinical phenotype.

Clinical data

Proband HBL-201 was a 13-year-old boy of Turkish ancestry born to consanguineous parents (first cousins) who was referred to the hospital for the incidental finding of a mild elevation of serum transaminases (alanine amino transferase [ALT] 47 U/L and aspartate amino transferase [AST] 40 U/L; reference range, 0-34 U/L). He looked healthy and did not have any complaint. His motor and cognitive milestones had been normal. The school performance was satisfactory. The result of physical examination was negative. His weight (37 kg) and height (148 cm) were at the 25th percentile for age (body mass index, 17.3 kg/m^2). Viral markers, sweat test, ceruloplasmin, and α-1 antitrypsin levels were in the normal range. Autoimmune hepatitis was ruled out. Acanthocytosis was not observed in peripheral blood smear. Abdominal ultrasonographic examination showed the presence of a mild liver enlargement and a moderate increase in liver echogenicity consistent with fatty liver. Fecal fat content was within the normal values. The result of ophthalmologic examination was negative, with no evidence of retinitis pigmentosa. The plasma levels of vitamin A and vitamin E were 1.83 μmol/L (reference range, 1.1–2.86 μmol/L) and 13.25 μmol/L (reference range, 15.3–33.1 μmol/L), respectively.

Table 1 shows the plasma lipid profile of the proband and his family. The proband's profile was characterized by very low levels of total cholesterol, LDL-C, triglyceride, and apoB. Total cholesterol and LDL-C levels in the parents and the sister of the proband were below the fifth percentile of the Turkish population. The presence of a lipid profile consistent with heterozygous FHBL in the parents suggested the hypothesis that the proband might have Ho-FHBL.

Supplementation with vitamin E and vitamin A was started on the assumption that this treatment would prevent

Table 1 Plasma lipid profile of HBL-201 patient and his family

Subject	Age (y)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	apoB (g/L)	apoE genotype
Mother	30	92	20	70	10	nd	ε3ε3
Father	37	100	43	52	25	nd	ε2ε3
Patient	13	71	10.2	58.6	11	<0.23	ε3ε3
Sister	4	77	35.5	35.1	32	0.23	ε2ε3
Reference range		70–175	60–130	35–75	35–110	0.55–1.4	

apoB, apolipoprotein B; apoE, apolipoprotein E; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; nd, not determined; TC, total cholesterol; TG, triglyceride.